REMARKS

Reconsideration of the above-identified application is respectively requested in view of the above amendments and the following remarks. The Examiner objected to claims 1, 19, and 88 and rejected claims 1, 5, 9, 10, 14, 19, 24, 25, 85-89 for multiple reasons. Claims 5, 9, and 19 have been withdrawn without prejudice. Claims 1, 88, and 89 have been amended. No new matter has been added with these amendments. The support for the amendments and for the newly added claims may be found in the original claims and in Examples of the application. Claims 1, 10, 14, 24, 25, and 85-91 are now in this case.

Applicant's invention is directed to *inter alia* a medical system for treating a spinocerebellar ataxia type 1 in a human live patient comprising: (a) an intracranial access device; (b) a mapping means for locating a predetermined location in the brain of the patient, said location comprising cells natively expressing a gene encoding an ataxin-1 protein; (c) a deliverable amount of a small interfering RNA capable of reducing the amount of ataxin-1 protein produced in said cells, or a vector encoding said small interfering RNA; and (d) a delivery means for delivering said small interfering RNA or vector encoding said small interfering RNA to said location of the brain of said patient from said intracranial access device through a stereotactically implanted catheter, wherein one strand of the small inhibitory RNA is complementary to a portion of the gene encoding the ataxin-1 protein located at least about 9 bp downstream of a transcription start site of said gene.

Priority

The Examiner has asserted that the priority application (Provisional Patent Application no. 60/429,387) does not support claims directed to medical systems comprising small interfering RNA and thus Applicant is not entitled to the 2002 filing date of Provisional Patent Application no. 60/429,387. The Examiner does acknowledge, however, that Provisional Patent Application no. 60/444,614, filed on February 3, 2003 provides adequate support for claims drawn to medical systems comprising small interfering RNA. Accordingly, Applicant withdraws the claim to domestic priority to Provisional Patent Application no. 60/429,387 filed on November 26, 2002, but maintain

the claim for domestic priority to Provisional Patent Application no. 60/444,614, filed on February 3, 2003 under 35 U.S.C. § 119(e).

Claim Objections

The Examiner objected to claims 1 and 88 because of grammatical informalities. Applicant has amended the objected claims in accordance with the Examiner's request. Accordingly, Applicant respectfully requests that the Examiner withdraw these objections.

Rejection Under 35 U.S.C. § 112 ¶2

The Examiner rejected claims 1 and 89 as being allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. Claim 89 has been amended in accordance with the Examiner's request.

The Examiner rejected claim 89 because, in his opinion, the disclosure would not inform a person of ordinary skill in the art about the meaning of the term "stably interact," as used in the claim. Without agreeing with the Examiner's assertions but in the interest of an expedited prosecution, applicant amended claim 89 to remove the phrase "stably interact" from the claim language. Accordingly, applicant respectfully requests the Examiner to withdraw this ground for rejection. The language of claim 89 is now consistent with, for example, the language of claim 1 found in issued U.S. Patent 7,022,828, concerning a different invention but pertaining to small interfering RNA and using a description of small interfering RNA that presumably inform a person of ordinary skill in the art about the meaning of the claim.

The Examiner further rejected claim 1 for the insufficient antecedent basis for the phrase "said patient." Applicant thanks the Examiner for pointing out this typographical error. Claim 1 has now been amended to correct this typo. Accordingly, applicant respectfully requests the Examiner to withdraw this ground for rejection.

Rejection Under 35 U.S.C. §112¶1

The Examiner rejected claims 1, 5, 9, 10, 14, 19, 24, 25, 85-89 as allegedly failing to comply with the written description requirement. The Examiner asserts that this ground of rejection is proper for two reasons: first, the specification did not describe

"mapping means", and second, the application does not describe "the genus of the siRNA molecules capable of inhibiting the expression of all genes responsible [for] all neurodegenerative disorders, or even all genes responsible for spinocerebellar ataxia type 1." *Office Action at 7.*

Applicant respectfully disagrees. First, the meaning of the term "mapping means" especially with regard to accessing (e.g., surgically accessing) the brain of a live human patient is well-understood in the art. In fact, in 2001, Medtronic introduced a "mapping means" device termed the Medtronic NT StealthStation® Treon™ into the marketplace. (Exhibit 1, attached hereto.) This medical system further refines the computerized technologies of multi-dimensional imaging and navigation to enable neurosurgeons to precisely plan, re-plan and visualize a procedure as it proceeds deep within the brain for treating a neurological disorder such as for example SCA1 in a living human patient.

In addition, a Micropat search of the US granted patents, US published application, WIPO publications and EPO granted patents and EPO published applications for the terms ((cranial or brain) and mapping means) returned over 150 references.

The Examiner himself describes the disclosures by Morel et al. and Serra et al. *Office Action at 24.* Specifically, the Examiner asserts as follows:

> Serra et al. describe technological improvements for surgery in human brains, comprising the use of ST and MR imaging, and the incorporation of detailed stereotactic atlases compiled over the years into their system of hardware and software for planning and carrying out neurosurgery. For example, Serra et al. describe an "electronic brain atlas" for identifying brain targets (page 320). Serra et al. describe the use of their system to target brain structures with almost any art-recognized surgical instrument, including probes and delivery devices. Accordingly, Serra et al. provide a detailed blueprint and disclose devices and software, and refer to several print publications, describing, teaching, and showing the use of stereotactic atlases to identify and locate virtually any target in the human brain.
>
> One of skill interested in particular region of the human brain, may, in addition to referring to Serra et al., use the teachings of Morel et al., among others, who teach a detailed atlas of human thalamus. Morel et al. teach that the thalamus is a major target for surgical treatment, given its prominence in cognitive functions and association with pathophysiological disorders (page 588). Morel et al. teach that computer tomography and magnetic resonance imaging-guided stereotaxy and preoperative microelectrode recordings for localization of targets has aided stereotactic neurosurgery. Morel et al. present a detailed map of the human thalamus,

> including several important subthalamic structures (page 589), and Appendix), and teach the importance of adapting such atlases to different brain sizes.

The Examiner further asserts that "Morel at al. and Serra et al. are considered to be representative of the state of the prior art regarding the level of skill and knowledge available to those in field of neurology and neurosurgery." *Id.* Thus, a person of the ordinary skill in the art (e.g., a neurosurgeon) would immediately recognize the meaning of the term "mapping means." Therefore, for at least this reason, applicant respectfully requests the Examiner to withdraw this ground of rejection.

Second, claim 1, as currently amended, is drawn to spinocerebellar ataxia type 1 and to a gene encoding the ataxin-1 protein. Thus, it cannot be asserted that claim 1 is drawn to siRNA capable of inhibiting the expression of ALL genes responsible for ALL neurodegenerative disorders. It is unarguable that the applicant was in possession of siRNA molecules capable of inhibiting expression of the ataxin-1 gene, as well as vectors encoding such siRNA molecules. For at least this reason, applicant respectfully requests the Examiner to withdraw this ground of rejection of claim 1.

Claims 10, 14, 24, 25, and 85-89 depend on claim 1 and were rejected for the same reasons. In view of the arguments and the amendments above regarding claim 1, applicant respectfully requests the Examiner to withdraw this ground of rejection of claims 10, 14, 24, 25, and 85-89.

Provisional obviousness-type double patenting rejection

The Examiner further rejected claims 1, 9-15, 19, and 25 under the judicially created doctrine of obviousness-type double patenting, as being unpatentable over claims 7, 8, 16, 17, and 29 of a co-pending application No. 10/962,732.

MPEP § 804(I)(B)(1) recites as follows:

> [i]f a 'provisional' nonstatutory obviousness-type double patenting (ODP) rejection is the only rejection remaining in the earlier filed of the two pending applications, while the later-filed application is rejectable on other grounds, the examiner should withdraw that rejection and permit the earlier-filed application to issue as a patent without a terminal disclaimer."

Applicant respectfully notes that the instant application was filed on 11.25.2003, while application No. 10/962,732 was filed later, on 10.12.2004. Therefore, the instant application is the earlier-filed application of the two applications. Applicant further notes that as of November 1, 2006, no action on merits have been taken regarding the later-filed application No. 10/962,732.

Accordingly, without making any admissions or agreeing with the Examiner, Applicant respectfully requests postponement of any action on this ground of rejection until this is the only ground for rejection of either claims 1, 9-15, 19, and 25 of the instant application or claims 7, 8, 16, 17, and 29 of a co-pending application No. 10/962,732.

Rejection on the basis of 35 U.S.C. §103

The Examiner has rejected claims 1, 9, 10, 14 and 24 under 35 U.S.C. § 103 as being allegedly unpatentable over Xia et al. (2002) *Nature* 20:1006-1010; Driscoll et al. (WO 01/49844); Cahill et al. (previously cited); Paxinos et al. (2001) *The Mouse Brain in Stereotaxic Coordinates.* Academic Press, 2nd Ed; Serra et al. (1996) *Medical Image Analysis* 1(4):317-329; Morel et al. (1997) *J. Comparative Neurology* 387-:588-630; Clark et al. (1997) *J. Neuroscience* 17:7385-7395; and Salehi et al. (1999) *J. Neural Transm.* 106:955-986.

Xia et. al. discloses a method of inhibiting expression of a transgene using a syringe to inject a vector comprising a siRNA sequence into the striatum of transgenic mice. Xia emphasizes that the siRNA sequence must be less than 30 nucleotides in length.

Contrary to Xia, Driscoll discloses that the siRNA should be between 20 nucleotides and over 1,000 nucleotides, and the siRNA is expressed from a vector to suppress expression of GFP in *C. elegans*. Applicant respectfully notes that while Driscoll provides some disclosure as to how to make vectors associated with neurodegenerative disorders, Applicant could not find any particular teaching of delivery systems and how to deliver these molecules to particular targets, or any suggestion of the usefulness to consider these factors. Driscoll does not teach or suggest the need to have an intracranial access device, a mapping means, or use of the device with the mapping means to direct delivery of the siRNA to predetermined locations of the brain.

Paxinos and Cahill disclose anatomical atlases of mouse and human brains, respectively, which the Examiner interprets as mapping means. At best, these references disclose laundry lists of brain structures and their relative locations. These references do not teach or suggest which brain structures, let alone any brain structure that are important for siRNA therapy of the neurodegenerative diseases, nor do they disclose which structures endogenously express genes responsible for the neurodegenerative disorders.

The disclosures of Morel et al. and Salehi et al. have been discussed above. These disclosures deal with the "mapping means" aspect of the invention and do not cure the deficiencies of Xia et al., Driscoll et al., Cahill et al., and Paxinos et al.

Clark et al. discloses a connection between spinocerebellar ataxia type 1 and the Purkinje cells, particularly those in the cerebellar cortex. Clark et al. does not discuss either siRNA therapy of spinocerebellar ataxia type 1, the criteria for siRNA selection or the specific siRNAs useful for treatment of spinocerebellar ataxia type 1. Thus, Clark et al does not add to the deficiencies of Xia et al., Driscoll et al., Cahill et al., Paxinos et al. Morel et al. and Salehi et al.

Thus, claim 1 is not obvious in view of the references cited by the Examiner. There is no motivation, except the impermissible hindsight, to combine the references. A person of ordinary skill in the art would not be motivated to create the siRNAs or vectors encoding such siRNAs as recited in claim 1 in its currently amended form on the basis of the references cited by the Examiner.

Applicant respectfully requests that the Examiner withdraw this ground for rejection of claim 1.

Claims 10, 14, and 24 depend on claim 1 and thus include all limitations of claim 1. Since the combination of references suggested by the Examiner does not make obvious claim 1 as currently amended, such combination of references does not make obvious the claims dependent from claim 1. MPEP § 2143.03. For at least these reasons, Applicant respectfully requests that the Examiner withdraw his rejection of claims 10, 14, and 24 under 35 U.S.C. § 103(a).

Rejection on the basis of 35 U.S.C. §103

The Examiner further rejected claims 1, 5, 9, 10, 14, 19, 24, 25, 85-87 and 89 under 35 U.S.C. §103 (a) as being unpatentable over Xia et al. (2002) *Nature* 20:1006-1010; Driscoll et al. (WO 01/49844); Paxinos et al. (2001) *The Mouse Brain in Stereotaxic Coordinates.* Academic Press, 2nd Ed; Cahill et al.; Serra et al. (1996) *Medical Image Analysis* 1(4):317-329; Morel et al. (1997) *J. Comparative Neurology* 387-:588-630; Clark et al. (1997) *J. Neuroscience* 17:7385-7395; and Salehi et al. (1999) *J. Neural Transm.* 106:955-986, as applied to claims 1, 9, 10, 14 and 24, above, and further in view of Whitesell et al. (1993) *Proc. Natl. Acad. Sci.* 90:4665-4669; Davidson et al. (US Patent Application Publication 2004/0023390); Matilla et al. (1998) *J. Neuroscience* 18:5508-5516; and Exhibit A: NCBI published mRNA sequence of SCA1 (Mar. 24, 1999).

The shortcomings of Xia et al.; Driscoll et al.; Cahill et al.; Paxinos et al.; Serra et al.; Morel et al.; Clark et al.; and Salehi et al. have been discussed above. The Examiner's further reliance on additional secondary references does not cure the infirmities in Examiner's argument.

The Examiner cites Whitesell et al. for a system for intraventricular administration of radioactively or fluorescently labeled antisense oligonucleotides into rats (pages 4665-6). The Examiner asserts that Whitesell discloses that the rats had a 22-gauge steel catheter stereotactically implanted in the lateral ventricle through which labeled antisense oligonucleotides were injected by bolus injection with a Hamilton syringe or continuous injection using a mini-osmotic pump (page 4666). Whitesell does not disclose a possibility of treatment of spinocerebellar ataxia type 1, Whitesell does not disclose the brain structures natively expressing the ataxin-1 gene, and finally, Whitesell does not provide any criteria for selection of the siRNAs such as those of the instant invention. In conclusion, Whitesell does not cure the deficiencies of the combination of Xia et al.; Driscoll et al.; Cahill et al.; Paxinos et al.; Serra et al.; Morel et al.; Clark et al.; and Salehi et al.

Davidson discloses a method of inhibiting expression of a transgene using parental administration to inject a vector comprising a siRNA sequence into the brain. Davidson like Xia (Xia is a co-inventor on Davidson) also emphasizes that the siRNA sequence must be less than 30 nucleotides in length. Davidson is inapposite to the instantly claimed invention for the following additional reasons: 1) The claims in

Davidson patent application are limited to short, hairpin DNA encoding for shRNA wherein the transcription of the shRNA is driven by an RNA polymerase type II promoter (such as CMV). In contrast, of course, Applicant's invention is not limited to the use of shRNA versus siRNA, let alone the use of RNA polymerase type two (pol II) promoters to drive the transcription of the shRNA.; 2) Davidson does not claim a medical system for treating a patient, nor does it teach a method for administering the treatment of SCA1 to the patient in terms of delivery devices, catheters, or specific anatomical regions to which to deliver the treatment; 3) Davidson does not provide any specific shRNA sequences that are effective at reducing the expression of the SCA1 mRNA in the patient.

Thus, Davidson does not cure the deficiencies of the combination of Xia et al.; Driscoll et al.; Cahill et al.; Paxinos et al.; Serra et al.; Morel et al.; Clark et al.; Salehi et al. and Whitesell et al.

The Examiner cites Matilla et al. for providing the motivation to create systems for delivering SCA1 targeting siRNAs into the brains of mice or rats arguing that Matilla et al. discloses that SCA1 has a genetic basis involving the expression of a mutant or toxic form of an SCA1 gene in Purkinje cells of the brain causing loss of these cells and an ataxic phenotype (page 5508). Matilla only discloses that knocking out SCA1 gene function from embryonic conception does not cause an ataxic phenotype in the developing or adult animal, indicating that the SCA1 disease in humans is not due to a loss of the function of the SCA1 gene or ataxin-1 protein. Matilla does not teach or suggest suppression of the expression of the SCA1 gene in patients as a means of treating the disease. No suggestion is provided to explore siRNA technology as a means for doing so. Further, Matilla does not disclose or suggest any criteria for selecting suitable siRNA molecules. Finally, no disclosure or suggestion is provided to administer siRNA in the areas endogenously expressing SCA-1. Thus, Matilla does not cure the deficiencies of the combination of Xia et al.; Driscoll et al.; Cahill et al.; Paxinos et al.; Serra et al.; Morel et al.; Clark et al.; Salehi et al., Whitesell et al. and Davidson et al.

Exhibit A: NCBI published mRNA sequence of SCA1 only provides a sequence for the ataxin-1 gene. However, this reference does not disclose or suggest treatment of the spinocerebellar ataxia type 1, nor does this reference disclose the brain areas where this sequence is expressed, nor the portions of this sequence suitable for siRNA targeting.

Thus, this reference does not cure the deficiency of the combination of the other eleven references cited by the Examiner.

In conclusion, the combination of the references cited by the Examiner will not teach or suggest all limitations of claim 1 in its currently amended form. MPEP § 2143.03 requires that "[T]o establish the *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art." The Examiner has not shown that this requirement is fulfilled.

Further, the combination of the references cited by the Examiner does not suggest the desirability of the siRNAs of the instant invention. MPEP § 2143.01 states that the prior art must suggest the desirability of the claimed invention.

For at least these reasons, Applicant respectfully requests that the Examiner withdraw this ground for rejection of claim 1.

Claims 10, 14, 24, 25, and 85-91 depend on claim 1 and thus include all limitations of claim 1. Since the combination of references suggested by the Examiner does not make obvious currently amended claim 1, such a combination of references does not make obvious the claims dependent from claim 1. MPEP § 2143.03. For at least these reasons, Applicant respectfully requests that the Examiner withdraw his rejection of claims 10, 14, 24, 25, and 85-91 under 35 U.S.C. § 103(a).

Applicants respectfully submit that the pending claims are valid and favorable reconsideration and allowance are earnestly solicited. If, however, for any reason the Examiner does not believe that such action can be taken at this time, it is respectfully requested that the Examiner telephone Applicant's attorney at (609) 844-3020 to discuss any additional rejections.

The USPTO is authorized to charge Deposit Account No. 50-1943 for any charges in connection with this matter.

Respectfully submitted,

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